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(54) METHODS OF CONTRACEPTION AND CONTRACEPTIVE COMPOSITIONS

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to methods of contraception, to contraceptive compositions and to processes for making these compositions. More particularly it is concerned with methods employing and compositions containing 1-enantiomorphs of certain 13 - alkylgona-1,3,5(10) - trienes, which are useful for preventing conception or pregnancy in warm blooded, ovulating vertebrates.

It is a matter of common knowledge and experience to adminster orally oestrogens/progestogens in admixture or sequentially to ovulating vertebrates to prevent ovulation. The desired objective in nearly all instances, following daily administration of unit dosages of such well-known progestogens as norethindrone or norethynodrel and such well-known oestrogens as mestranol or ethynyloestradiol, is to inhibit the production or release of gonadotropins from the pituitary and to suspend ovulation, thus preventing conception. In this manner, in live-bearing species, a luteoid endometrium is induced and maintained while the composition is taken for the inhibition of ovulation, that is, prevention of conception, and normal cyclic alterations may be induced.

Somewhat less well-known is a means to prevent conception by administration of a progestogen alone, on a daily basis, and often in very small amounts (the so-called "micro doses"). The exact mode-of-action of such materials is not entirely understood, but contraception has been demonstrated at dose levels that do not appear to alter pituitary function and thus do not inhibit ovulation. It is currently believed that agents of this type are effective by preventing the liquefaction of cervical mucus that occurs at about the time of ovulation in primates. Failure of the mucus to change in the "normal" way results in prevention of sperm migration into the uterus (of live-bearing species) and a prevention of impregnation. In these circumstances, the sperm do not migrate through the endo-cervical canal. To use this latter method to prevent conception, it has up to now been essential to administer the progestogens on a daily basis and recent reports by workers in this field suggest that duration of cervical action of certain progestogens is even less than 24 hours. As a result of the necessity for daily dosage (pill)-administration, the patient-failure rate has been high for this approach to contraception and method-failure rate has also been relatively high (compared with conventional oral contraceptives, first above-mentioned), presumably as a result of the short duration of action. Normal sperm migration through the reproductive tract of mammals to the site of fertilisation depends in part upon the characteristics of the cervical mucus, which are produced by the action of oestrogens on the cervical glands. Anti-oestrogens modify the characteristics of the mucus and prevent migration of the spermatozoa. To date only progestational anti-oestrogens are so employed.

All the oestrogens used previously have been steroids of the natural configuration, and all the progestogens have been steroids of the natural configuration, or in some instances racemates in which the enantiomer of the natural configuration is the active ingredient. We have now surprisingly found that *l* - enantiomorphs of certain 13 - alkylgona - 1,3,5(10)-

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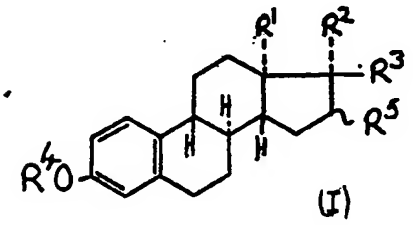
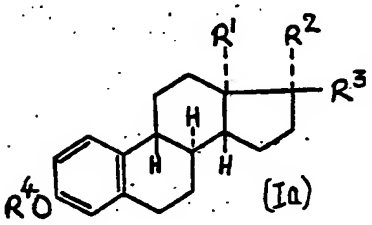
trienes are effective in preventing conception or pregnancy in warm-blooded ovulating vertebrates. Accordingly, the present invention provides a method of preventing pregnancy in a warm-blooded ovulating vertegrate which comprises the administration thereto of a compound of general formula I



(I)

wherein R^1 is (lower)alkyl; R^2 is hydroxy or (lower)alkanoyloxy and R^3 is hydrogen, (lower) alkyl, (lower)alkenyl or (lower)alkynyl or R^2 and R^3, taken together, are $=O$; R^5 is hydrogen or hydroxy; and the wavy line at the 16-position indicates α- or β-configuration, said compound being substantially free from the corresponding *d*-enantiomorph.

The invention also provides a contraceptive composition comprising a compound of general formula (Ia)



(Ia)

wherein R^1 is (lower)alkyl; R^2 is hydroxy or (lower)alkanoyloxy and R^3 is hydrogen, (lower) alkyl, (lower)alkenyl or (lower)alkynyl or R^2 and R^3, taken together, are $=O$; and R^4 is hydrogen or (lower)alkyl; said compound being substantially free from the corresponding d-enantiomorph, and a pharmacologically-acceptable solid carrier suitable for oral administration.

The active compounds of general formulae (I) and (Ia) are 1-enantiomorphs, substantially free of the corresponding *d*-enantiomorphs. The d-enantiomorph of the natural series is the mirror image of the compound represented by the structural formula (I) or (Ia). There are two accepted ways of naming the active ingredients. According to the terminology of the Horeau-Reichstein Convention approved by Fieser or Fieser, Steriods, (1959) at page 336, the active compounds would be designated *l* - 3 - alkoxy- or -hydroxy - 13 - alkylgona-1,3,5(10) - trienes and the 16-hydroxy analogues thereof. A somewhat more recent and scientifically preferred system of nomenclature has been promulgated as a rule by the International Union of Pure and Applied Chemistry in Steroids, *13*, (3) 277—310, (1969). This rule will govern the naming of steroid compounds in learned papers submitted for publication in journals. In this system the enantiomer of a given steroid compound of the natural series is given the same name, preceded by the prefix "*ent*-". In the latter system of nomenclature it is readily apparent, therefore, that *l* - oestradiol would be called *ent*-oestradiol - 17β and that the active ingredients of general formula (I) would be designated *ent* - 3 - alkoxy- or -hydroxy - 13 - alkyl gona - 1,3,5(10) - trienes and the 16 - hydroxy analogues thereof.

The compositions of the present invention will, of course, contain sufficient active ingredient to impart contraceptive activity to the composition.

While the reasons for their effectiveness as contraceptives are not clearly understood at this time, it appears that the *l* - enantiomorphs (*ent*-forms) of general formula (I) act by virtue of their antioestrogenic effects. For example, because of their anti-oestrogenic activity the compounds may prevent migration of the sperm through the endo-cervical canal of mammals. Alternatively or additionally, it is known that normal implantation of the fertilised egg or zygote appears to depend on a brief surge of oestrogenic hormones to initiate the process. Oestrogenic antagonists such as the *l*-enantiomers of general formula (I) appear to inhibit implantation, leading unexpectedly to a most effective means of contraception.

The present invention permits administration of contraceptive agents on a much simplified basis in a highly effective manner accompanied by a minimum of side effects observed with the prior art methods. Thus, since the active compounds are ineffective and/or exceedingly weak as classical oestrogens, they will not produce the uterine hyperplasias caused by classical oestrogens nor will the bleeding problems that limit the use of progestogens be manifest.

Preferably each unit dosage of the composition comprises from about 0.05 mg. to about 20 mg. of active compound and a major proportion of the carrier.

The preferred active compounds are *l*-oestradiol (*ent* - oestradiol - 17β) and *l* - 18-homo oestradiol (*l* - 13β - ethylgona-1,3,5(10) - triene - 3,17β - diol) i.e. compounds of general formula (I) in which R^1 is methyl or ethyl, R^2 is hydroxy and R^3, R^4 and R^5 are hydrogen.

When used in this specification, the term

"warm-blooded ovulating vertebrates" contemplates female animals and birds such as humans, mice, rates, guinea pigs, rabbits, monkeys, gibbons, langurs and chickens, and valuable doestic animals and birds, such as dogs, cats, rabbits, sheep, cattle, horses, chickens and turkeys of such an age that ovulation is feasible and normal. The term "contraceptive composition" contemplates a composition which prevents pregnancy. Pregnancy may for example be prevented by a mechanism whereby the vertebrate does not produce a fertilised egg because the necessary contact with sperm has been inhibited. In this case contraception is prevented, in essence, by administration of an agent, which modifies the nature of the reproductive tract to such a degree as to provide an inappropriate environment for any sperm which might be present. Alternatively or additionally, pregnancy may be prevented by a mechanism whereby there is prevented implantation of the zygote in the vertebrate.

In the method of the invention the compound of general formula (I) may be administered in the form of a composition with the active ingredient in association with a pharmacologically-acceptable carrier.

The term "pharmacologically-acceptable carrier" contemplates usual and customary liquid and solid substances employed to formulate unit dosages for pharmacological purposes. It also will include in its broadest aspects, animal feedstuffs. In the compositions of the present invention and also preferably when in the methods of the invention the compounds is administered in the form of a composition, the carrier is a solid carrier suitable for oral administration.

The term "(lower)alkyl" contemplates alkyl groups from 1 to 10 carbon atoms, illustrative members of which are methyl, ethyl, *n*-propyl, *i* - propyl, *n* - butyl, *t* - butyl, *n*-pentyl, *n* - hexyl, cyclopentyl, *n* - octyl, *n*-nonyl and *n* - decyl. Derivations thereof, such as "(lower)alkenyl" and "(lower)alkynyl" contemplate analogous groups containing, respectively, a double bond and a triple bond. "(Lower)alkanoyloxy" contemplates groups derived from hydrocarbon carboxylic acids containing from two to ten carbon atoms, such as acetoxy, butanoyloxy, heptanoyloxy and decanoyloxy.

The compositions of the present invention may be prepared by brining the active compound of general formula (I) into association with the pharmacologically-acceptable carrier.

To formulate unit dosages for administration the active ingredient can be compounded into dosage forms, such as tablets and capsules. This is done by combining the active ingredient with conventional carriers, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting wax and cocoa butter. Diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders, tablet-disintegrating agents, and other conventional excipients may be employed. The active ingredient can be formulated with an encapsulting material with or without other carriers. In all cases, the proportion of active ingredient in the said compositions will be at least sufficient to impart contraceptive activity thereto on administration. For example, this may range upward from abour 0.001% by weight of active ingredient in said composition. As is mentioned above the amount of active ingredient especially preferred for each unit dosage (e.g. tablet or capsule) is from about 0.05 to 20 mg. of active ingredient [although from about 0.001 to about 100 mg. can be used, if desired].

The "active ingredients" contemplated by this invention are *l* - enantiomorphs of natural and synthetic steroidal oestrogens, specifically, 3 - (lower)alkoxy or hydroxy - 13 - alkylgona-1,3,5(10) - trienes of general formula (I) hereinabove, which can be prepared by procedures well within the capabilities of those skilled in the art. For example, the compounds can be prepared by resolution of the racemates of the compounds of the invention and their *d*-enantiomers or by resolution of racemic intermediates from which the active compounds can be prepared by known procedures. The racemic starting materials can be prepared by total steroid syntheses as described in the literature. The active compounds can also be prepared by treating with acid or base, the corresponding 1,β - hydroxygon - 4 - ene - 3 - one steroids of the 1 - series compounds (II) many of which are described in U.S. Patent specification 3,231,589. The compounds (II) may be prepared by microbiological oxidation, by the process described in U.S. Patent specification, 3,231,589, of gon - 4 - en - 3 - one starting materials (for example, those described in Belgian Patents 623,844 and 608,370). Steroids of general formula (I) may, for example, be prepared by placing a starting material such as the compound (II) in a solvent and treating with a selected acid or base. Treatment with acid or base in this manner brings about dehydration accompanied by an aromatisation of the A-ring. In treating the compound (II) with acid according to this method, the compound may be placed in a solvent such as acetone and treated with a mineral acid such as hydrochloric acid for a short period of time such as from about 1 to about 3 minutes. The solution can then be poured into ice water and extracted with a solvent such as for example chloroform. The extraction can then be evaporated to dryness. The product may then be recrystallised as desired according to conventional techniques. In utilising base to effect the dehydration-aromatisation, the selected compound II can be dissolved in a solvent such as methanol.

If desired the methanol may be heated to decrease the amount of solvent necessary to dissolve the steroid. A dilute solution of base is then added to the steroid to effect the dehydration-aromatisation. The addition of acid will cause precipitation of the desired product which may then be recrystallised as desired. If the product of general formula (I) of the above processes is not that required, the desired compound can be obtained by conventional after-processes. For example, a compound in which R^2 is hydroxy and R^3 is hydrogen can be oxidised to a compound in which R^2 and R^3 taken together are $=O$ and the latter compound can be reacted with an organo metallic reagent to give a compound in which R^3 is alkyl, alkenyl or alkynyl and R^2 is hydroxy. Detached procedures for the preparation of exemplary active ingredients contemplated by this invention will be given hereinafter.

As is mentioned hereinabove, the instant active ingredients possess marked intrinsic anti-oestrogenic activities with a complete lack of progestational effects and relative to classical oestrogens they are ineffective and/or exceedingly weak. They do not produce the bleeding problems that limit the use of progestogens and will not cause uterine hyperplasias.

One pharmacological test in which the anti-oestrogenic effectiveness of one of the instant active ingredients is demonstrated was as follows: The administration of natural *d* - oestradiol (oestradiol - 17β) to immature mice is followed by uterine growth and vaginal opening. These processes are reversed by the simultaneous administration of *l* - oestradiol (*ent*-oestradiol - 17β):

Total dose (μg)			Mean Uterine Wt.	Number with Open
d-Oestradiol	*l*-Oestradiol	*N*	($\pm$ S.E.)	Vaginae
Oil controls		16	14.6 $\pm$ 1.29	0
0.1	0	16	30.4 $\pm$ 2.39	10
0.1	1	16	30.0 $\pm$ 2.14	12
0.1	10	16	25.4 $\pm$ 1.62	3
0.1	100	16	18.4 $\pm$ 0.99	4

Another pharmacological test in which the anti-oestrogenic activity of one of the instant active ingredients is demonstrated was as follows: *d* - Oestradiol (oestradiol-17β) will also induce cornification of the vaginal epithelium of spayed adult mice, a process that is also reversed by *l* - oestradiol (*ent* - oestradiol-17β):

Total dose (μg)			%
d-Oestradiol	*l*-Oestradiol	*N*	Positive Smears
1	0	24	71
1	1	10	80
1	10	10	70
1	100	9	88
1	300	13	46
1	1000	24	25
1	3000	8	25

The impotence of *l*-oestradiol (*ent*-oestradiol-17β) as a classical oestrogen is demonstrated by the following data:

Total Dose (μg)	N*	*d*-Oestradiol Uterine Wt.	N*	*l*-Oestradiol Uterine Wt.
Controls	4	18.2 mg.	5	17.8 mg.
0.01	2	29.0		
0.03	5	33.2		
0.1	4	38.5	2	19.5
0.3	3	41.7	2	15.5
1.0			2	19.0
10.0			4	15.5
30.0			2	15.5
100.0			3	15.7
300.0			2	16.5
1000.0			2	26.0

*N = groups of 7—8 rats pooled for cited mean uterine weights. Thus 1000 μg. of *l*-oestradiol is less uterotrophic than 0.01 g. of oestradiol.

The conception preventing efficacy is further demonstrated pharmacologically as follows: Nineteen female rats were smeared vaginally one day pre-injection and divided into two groups the following day:

Group I (8 rats) received oil subcutaneously.

Group II (11 rats) received *l* - 13β - ethyl-gona - 1,3,5(10) - triene - 3,17β - diol, 1 mg, subcutaneously.

The rats were injected and vaginally smeared daily. None of them (either control or test) showed classical 4 or 5 day cycles. On the seventh day of injection, males were introduced into the cage. Injections and smears were discontinued when the female mated (presence of sperm in smear on Day one). Females were autopsied on Day 14: All females had mated by the third day after the males were added. The following chart shows the number of females mating in both groups on days one, two and three after the males were added.

Day	Oil Only	Oil and Test Compound
1	3	9
2	3	1
3	2	1

All of the eight control animals were pregnant with an average of eleven normal pups. None of the eleven compound treated rats were pregnant.

Thus the test compound is effective in preventing conception.

Still another pharmacological test to demonstrate the valuable utility of the active compounds comprises the so-called "Claudogen assay". Adult female Charles River rats are caged week days with males in colonies of eight females and four males. Vaginal smears are taken after each night of cohabitation, and the presence of sperm in the smears is used as an index of mating and the initiation of pregnancy. Treatment sub-cutaneously with the compound of interest in an aqueous vehicle is begun on the day that sperm are present

in the smear (day 1 of pregnancy) and continued until day 7. The female rats are sacrificed on day 14 and inspected for "normal" fetal development. Rats containing at least one "normal" fetus are considered pregnant. In this test, using an oil control, 5 out of 5 of the test animals become pregnant. Using one of the active ingredient of this invention, *1*-oestradiol (*ent* - oestradiol - 17β), at one mg./animal/day, 0 out of 5 animals become pregnant; and using another active ingredient of this invention, *1* - 13β - ethylgona - 1,3,5(10)-trien - 3,17β - diol (*ent* - 13β - ethylgona-1,3,5(10) - trien - 3,17β - diol), at one mg./animal/day and at 10 mg./animal/day, 0 out of 5 animals became pregnant, respectively.

The following procedures illustrate the preparation of active ingredients employed in the present invention.

Procedure A

1 - Oestradiol (1 - 13β - methylgona-1,3,5(10) - trien - 3,17β - diol)

A solution of 965 mg. of *1* - 13β - methyl-1β, 17β - dihydroxy - 4 - gonen - 3 - one (prepared by the general procedure described in U.S. 3,231,589) in 400 ml. of 0.1 *N* sodium hydroxide solution and 300 ml. of methanol is heated to 50°C. and filtered. The residue is dissolved in methanol, filtered, and the filtrate combined with the first filtrate. After 30 minutes, 10% hydrochloric acid is added to adjust the pH to 6.2, which causes precipitation of the product, which is filtered. It is recrystallised from aqueous methanol ether acetone, ether and benzene, m.p., 177—178°C.

Procedure B

1 - 13β - ethylgona - 1,3,5(10) - trien-3,17β - diol

The method of Procedure A is repeated, substituting the corresponding 13β - ethyl-1β - ol and the product, m.p. 189.5—190°C. is obtained.

Procedure C

1 - 13β - ethyl - 3 - methoxygona - 1,3-5(10) - trien - 17β - ol

A solution of 1.266 g. of *1* - 13β - ethylgona - 1,3,5(10) - trien - 3,17β - diol in 40 ml. of boiling ethanol is treated four times with 7.2 ml. of 60% sodium hydroxide solution and 10 ml. of dimethyl sulphate. After the final adition, the solution is cooled and 100 ml. of water is added. The mixture is cooled in ice for 30 minutes and filtered. The solids, 1.364 g., are identified as the methyl ether by thin-layer chromatography. Chromatography over silica gel (elution with 2% ethyl acetate in benzene) and recrystallisation from methanol affords *1* - 13β - ethyl - 3-methoxygona - 1,3,5(10) - trien - 17β - ol, m.p. 107.5—109.5°C. (Kofler): $[\alpha]_D$—50.8° (1% in chloroform); λ_{max} 222mμ (ϵ8.460), 282 mμ (ϵ2,100), 288 mμ (1.965); λ_{max}^{KBr} 3.06μ, 6.20μ, 6.35μ, 6.66μ.

Procedure D

1 - 13β - ethyl - 3 - methoxygona - 1,3,5(10)-trien - 17 - one

A solution of 3.94 g. of *1* - 13β - ethyl- 3-methoxygona - 1,3,5(10) - trien - 17β - ol in 300 ml. of acetone (system under nitrogen) containing 2.5 g. of anhydrous magnesium sulphate is treated with 5 ml. of a chromic acid solution (made from 2.67 g. of chromium trioxide, 2.3 ml. of concentrated sulphuric acid, and diluted to 10 ml. with water) added dropwise over 15 minutes. After stirring for 15 minutes, 20 ml. of 2-propanol is added along with excess sodium bicarbonate, and after stirring for an additional five minutes, the mixture is filtered. The solids are washed with methylene chloride which washes are evaporated under vacuum to a slurry and 150 ml. of ether is added. The solution is washed three times with 15 ml. of water, dried over anhydrous magnesium sulphate, and evaporated under vacuum. The residue is dissolved in 150 ml. of boiling methanol, filtered and cooled overnight. The resultant crystals are filtered, yielding 2.7035 g. of *1* - 13β - ethyl - 3 - methoxygona - 1,3,5(10) - trien - 17 - one.

Procedure E

1 - 17α - ethynyl - 13 - ethyl - 3 - methoxygona - 1,3,5(10) - trien - 17 - ol

Under an atmosphere of acetylene there is placed 1.95 g. of lithium acetylide in 15 ml. of dioxane-ethylenediamine. The measuring vessel is washed out with 2 ml. of distilled dimethylacetamide and the washings added to the reaction flask. To this mixture is added 2.8623 g. of *1* - 13β - ethyl - 3 - methoxygona-1,3,5(10) - trien - 17 - one, as prepared in Procedure D, dissolved in 22 ml. of distilled dimethylacetamide. The reaction is stirred at room temperature for five hours, when it is poured onto 65 ml. of crushed ice. The mixture is extracted four times with 40 ml. of benzene; the benzene extracts are washed twice with 7.5 ml. of 10% sulphuric acid, four times with 10 ml. of water, and finally with 5 ml. of brine. The benzene extract is dried over anhydrous sodium sulphate and evaporated under vacuum, yielding an oil which is dissolved in 25 ml. of methanol, which is evaporated to *ca.* 15 ml. At this point 3 ml. of water is added. After cooling for several hours, the product is filtered yielding 2.5380 g. of the desired *1* - 17α - ethynyl - 13β - ethyl - 3-methoxygona - 1,3,5(10) - trien - 17β - ol.

Procedure F

1 - 13β - ethylgona - 1,3,5(10) - trien 3,16α,17β - triol

1 - 13β - ethyl - 1β,16α,17β - trihydroxy-4 - gonen - 3 - one, prepared by the general procedure of U.S. 3,231,589, is aromatised by Procedure A herein to provide the title compound.

Procedure G

1 - 13β - ethylgona - 1,3,5(10) - trien-3,16 ,17β - triol

1 - 13β - ethyl - 1β,16β,17β - trihydroxy-4 - gonen - 3 - one (prepared by the general procedure described in U.S. 3,231,589) is aromatised by Procedure A herein and the title compound is obtained.

The following examples illustrate the preparation of compositions of this invention and compositions which may be employed in the methods of this invention.

Example 1

A tablet for use in the prevention of conception or pregnancy is prepared from the following ingredients:

1 - oestradiol (*ent* - oestradiol-17β)	5 mg.
carboxymethylcellulose (400 cps)	15 mg.
lactose powder	25 mg.
redried corn starch	25 mg.
magnesium stearate powder	4 mg.
calcium silicate powder	q.s.
	200 mg.

The tablet is prepared by dissolving the steroid in benzene, mixing the solution with starch, drying the mix in a current of air, adding the remaining ingredients, mixing and compressing the composition into slugs. The slugs are regranulated and compressed into tablets, each containing 5 mg. of the *1*-enantiomorph.

Example 2

Tablets are prepared having the same composition as in Example 1, except that an equal weight of the *1* - enantiomorph of 13β - ethylgona - 1,3,5(10) - trien - 3,17β - diol is substituted for the *1* - oestradiol. The tablet is prepared by dissolving the steroid in benzene, mixing the solution with the lactose powder and drying the mix in a current of air, then adding the carboxymethylcellulose and half the starch. With the powder thus obtained is mixed starch paste prepared from the remainder of the starch, the mixture is wet-granulated, the granules dried, the stearate added and the composition compressed into tablets.

Example 3

A capsule for use orally to prevent conception or pregnancy contains, in encapsulating gelatin, the following ingredients:

1 - oestradiol (*ent* - oestradiol-17β)	5 mg.
finely divided silica lubricant	5 mg.
magnesium stearate powder	5 mg.
powdered corn starch	113 mg.
lactose powder	q.s.
	245 mg.

Example 4

Formulations for prevention of conception or pregnancy are prepared in tablet form consisting of the following ingredients:

	mg.				
l-oestradiol (*ent*-oestradiol-17β)	0.05	1.0	5.0	10.0	20.0
microcrystalline cellulose, N.F.	20.0	20.0	20.0	20.0	20.0
magnesium stearate, U.S.P.	0.22	0.22	0.22	0.22	0.22
lactose, U.S.P. q.s. ad	100.00	100.00	100.00	100.00	100.00

Example 5

Tablets for preventing conception or pregnancy are formulated and prepared according to Example 1 substituting for *1* - oestradiol, respectively, an equivalent amount of the following compounds:

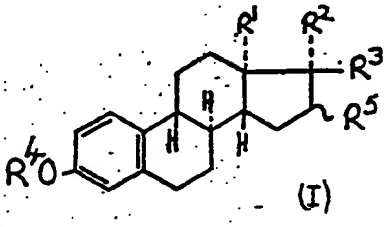
ent - 13β - ethyl - 3 - methoxygona-1,3,5(10) - trien - 17β - ol;
ent - 13β - ethyl - 3 - methoxygona-1,3,5(10) - trien - 17 - one; and
ent - 17α - ethynyl - 13β - ethyl - 3-methoxygona - 1,3,5(10) - trien - 17β - ol.

Tablets for preventing conception or pregnancy are formulated and prepared according to Example 1, substituting for *I* - oestradiol, respectively, an equivalent amount of the following 1 - enantiomorphs of general formula (I) in which R^1, R^2, R^3, R^4 and R^5 have the meanings:

R^1	R^2	R^3	R^4	R^5
CH_3	$OCOCH_3$	H	CH_3	H
$CH_3(CH_2)_8CH_2$	OH	H	H	H
CH_3	OH	CH_3	H	H
CH_3	OH	$CH=CH_2$	H	H
CH_3	OH	H	$CH_3(CH_2)_8CH_3$	H
CH_2CH_3	OH	H	H	α-OH
CH_2CH_3	OH	H	CH_3	β-OH

WHAT WE CLAIM IS:—

1. A method of preventing pregnancy in a warm-blooded ovulating vertebrate which comprises the administration thereto of a compound of general formula I



(I)

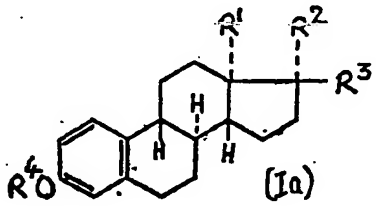
wherein R^1 is (lower)alkyl; R^2 is hydroxy or (lower)alkanoyloxy and R^3 is hydrogen (lower) alkyl, (lower)alkenyl or (lower)alkynyl or R^2 and R^3, taken together, are =0; R^4 is hydrogen or (lower)alkyl; R^5 is hydrogen or hydroxy; and the wavy line at the 16-position indicates α- or β-configuration, said compound being substantially free from the corresponding *d* - enantiomorph.

2. A method as claimed in Claim 1 wherein in the compound of general formula (I) R^1 is ethyl.

3. A method as claimed in Claim 1 or Claim 2 wherein in the compound of general formula (I) R^1 is ethyl, R^3 is hydroxy and R^3, R^4 and R^5 are hydrogen.

4. A method as claimed in Claim 1 wherein in the compound of general formula (I) R^1 is methyl, R^2 is hydroxy and R^3, R^4 and R^5 are hydrogen.

5. A contraceptive composition comprising a compound of general formula (Ia).



(Ia)

wherein R^1 is (lower)alkyl; R^2 is hydroxy or (lower)alkanoyloxy and R^3 is hydrogen, (lower) alkyl, (lower)alkenyl or (lower)alkynyl or R^2 and R^3, taken together, are =0; and R^4 is hydrogen or (lower)alkyl; said compound being substantially free from the corresponding *d*-enantiomorph, and a pharmacologically-acceptable solid carrier suitable for oral administration.

6. A composition as claimed in Claim 5 in which each unit dosage comprises from 0.001 to 100 mg. of compound of general formula (Ia) and a major amount of carrier.

7. A composition as claimed in Claim 5 or Claim 6 in which each unit dosage comprises from 0.05 to 20 mg. of compound of general formula (Ia) and a major amount of carrier.

8. A composition as claimed in any one of Claims 5 to 7 in the form of a tablet or capsule for oral administration.

9. A composition as claimed in any one of Claims 5 to 8 wherein in the compound of general formula (Ia) R^1 is methyl or ethyl, R^2 is hydroxy and R^3 is lower(alkyl), (lower) alkenyl or (lower)alkynyl.

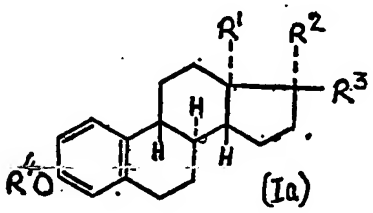
10. A composition as claimed in Claim 9 wherein R^1 is ethyl.

11. A composition as claimed in any one of Claims 5 to 8 wherein in the compound of general formula (Ia) R^1 is ethyl, R^2 is hydroxy and R^3 and R^4 are hydrogen.

12. A composition as claimed in any one of Claims 5 to 8 wherein in the compound of general formula (Ia), R^1 is methyl, R^2 is hydroxy, and R^3 and R^4 are hydrogen.

13. A contraceptive composition as claimed in Claim 5 substantially as hereinbefore described with reference to any one of the examples.

14. A process for preparing a contraceptive composition in which a compound of general formula (Ia)



(Ia)

wherein R^1 is (lower)alkyl; R^2 is hydroxy or (lower)alkanoyloxy and R^3 is hydrogen, (lower) alkyl, (lower)alkenyl or (lower)alkynyl or R^2 and R^3, taken together, are $=O$ and R^4 is hydrogen or (lower)alkyl; said compound being substantially free from the corresponding *d*-enantiomorph, is brought into association with a pharmaceutically acceptable solid carrier suitable for oral administration.

15. A process for preparing a contraceptive composition as claimed in Claim 14 substantially as hereinbefore described with reference to any one of the examples.

16. A method of preventing pregnancy in a warm-blooded ovulating vertebrate which comprises the administration thereto of a composition as claimed in any one of Claims 5 to 13.

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